REMARKS

Claims 34 and 72-79 are pending in the application and stand rejected. Official Action, Jan. 17, 2008. For at least the reasons presented below, applicants traverse the outstanding rejections and respectfully request reconsideration and withdrawal of all such rejections, further examination, and formal notification of allowance.

Applicants' Summary of the Interview

Applicants gratefully acknowledge the in-person interview conducted with Examiner Gembeh and Supervisory Examiner Marschel on February 22, 2008. The interview substantially advanced prosecution, and will expedite resolution of the issues.

During the interview, applicants distinguished the claimed invention over the cited art. Applicants pointed out that, to the extent that the art taught the use of a binding cellulose derivative, it taught that the binding cellulose derivative must be used at substantially greater concentration (e.g., ≥20% by weight of the pharmaceutical formulation). A patentable distinction is applicant's use of significantly lower quantities, and an associated reduction in food effect.

Applicants also pointed out that, as acknowledged in the Official Action, Curtet fails to disclose fenofibrate formulations comprising cellulose polymer, or the specified quantity of binding cellulose derivative. With regard to Boyer, applicants argued, and it was acknowledged, that those pharmaceutical formulations do not contain a surfactant; and do not contain a binding cellulose derivative at 12.5% by weight of the pharmaceutical formulation. With regard to Stamm, applicants argued, and it was acknowledged, that there is no disclosure of an HPMC binder at 5-40% by weight in a pharmaceutical formulation as claimed. Rather, Stamm teaches that to improve fenofibrate bioavailability, one should incorporate binding cellulose derivative at much higher concentration than that claimed. Thus, Stamm teaches away from the claimed range of binding cellulose derivative, which substantially reduces binding cellulose derivative relative to the prior art. Those and other arguments in support of the patentability of the pending claims are presented in more detail below.

Arguments in Response to Prior Art Rejections

Curtet, USPN 4,895,726

As acknowledged in the Official Action, Curtet fails to disclose fenofibrate formulations comprising cellulose polymer, or the quantity of binding cellulose derivative. The inclusion of binding cellulose derivative, at a specified quantity, is an express limitation of the claimed invention.

Further, Curtet teaches that to enhance bioavailability of fenofibrate, it must be co-micronized with a surfactant. Co-micronization is not an element of the pending claims. Applicants concede that the instant claims do not preclude co-micronization of fenofibrate with a surfactant; however, insofar as obviousness is concerned, Curtet teaches that the result-oriented variable that should be adjusted is co-micronization, not adjustments in binding cellulose derivative. As discussed above, the Curtet formulations do not include any binding cellulose derivative.

Curtet, either alone or in combination with other cited references, fails to teach or suggest the claimed invention.

Boyer, USPN 4,800,079

Boyer likewise fails to teach or suggest the claimed invention, either alone or in combination with the other cited references. The formulations of Boyer contain no surfactant, another express limitation of the instant claims. Boyer is also silent as to the relationship between cellulose derivative relative to the quantity of fenofibrate and/or the composition as a whole.

The rejection asserts that Boyer teaches incorporation of cellulose derivative at 12.5%; and, as that falls within the claimed range of binding cellulose derivative, it discloses the claimed limitation. The assertion mischaracterizes the reference.

Boyer teaches that in fabricating its fenofibrate compositions, there is a step wherein the inert core is coated with, among other things, "an alcohol solution containing 12.5% by weight of a methylacrylic polymer" to make the inert core damp and sticky. Boyer, col. 2, lines 52-55. Then, fenofibrate is sprayed onto the damp and sticky cores. Boyer, col. 2, lines 55-56. The alcohol solution of Boyer is not to be confused with the claimed formulation because, at the very least, it does not contain fenofibrate. Boyer's 12.5% solution of methylacrylic polymer in alcohol has no relation to the claimed pharmaceutical composition wherein binding cellulose derivative represents between 2-15% by weight of the composition. Accordingly, Boyer does not teach or suggest the claimed invention.

Further, the structure of the granules of the Boyer formulation is distinct from those claimed here. Notably, Boyer discloses the successive layering of an active agent on an inert core with the assistance of a binder. Specifically, an alcohol solution of a water soluble (hydrophilic) binder is applied to the surface of an inert core. Dry, microcrystalline fenofibrate is then added to the tacky binder layer; and the binder is quickly dried. If the tacky binder layer is not quickly dried, the microcrystalline fenofibrate particles will deform, and lose the dissolution benefits associated with the microcrystalline fenofibrate. The layering of binder and fenofibrate is repeated until the requisite quantity of fenofibrate has been applied to the inert core. Finally, the granules are coated with a protective layer. *See* col. 2, line 38 - col. 3, line 12.

Given Boyer's layering technique, and the resulting structure, there is no active layer in Boyer having fenofibrate, surfactant, and binding cellulose derivative, and wherein the binding cellulose derivative is 2-15% by weight of the combination of the neutral core, the fenofibrate, the surfactant, and the binding cellulose derivative.

Finally, the rejection fails to show how Boyer might be combined with any of the other references to teach or suggest the claimed invention. Notably, Boyer does not cure the deficiencies of Curtet in that it fails to teach or suggest any modification of either formulation resulting in the combined ingredients of the instant claims. Even if one were to arrive at such a combination, there has been no showing that the references teach or suggest the relative quantities claimed. Accordingly, Boyer fails to cure the deficiencies of Curtet, and vice versa.

Stamm, USPN 6,074,670

Stamm is also distinguishable, and it fails to cure the deficiencies of either of Boyer or Curtet.

Stamm describes pharmaceutical formulations containing micronized fenofibrate, surfactant, and a binder of hydroxypropylmethylcellulose (HPMC). The rejection asserts that Stamm teaches a pharmaceutical formulation as claimed comprising HPMC at 5-40%, and that the disclosed range overlaps with the claimed range of binding cellulose derivative. Again, this is a mischaracterization of the reference.

As in Boyer, Stamm's reference is to an intermediate processing step using a suspension to fabricate the ultimate pharmaceutical formulation. Stamm, col. 6, lines 16-37. That suspension is not a pharmaceutical formulation as in the instant claims, and does not contain the claimed elements. As such, the HPMC quantitative calculation is made relative to a separate solvent-containing suspension, not a pharmaceutical composition as claimed. Accordingly, Stamm does not teach or suggest the claimed invention, either alone or in combination with any of the other cited references.

In a paragraph bridging columns 4 and 5, Stamm describes various components that can be included in its formulation. Among those is a hydrophilic polymer. As used by Stamm, the term "hydrophilic polymer" is defined at col. 4, lines 14-21. Examples include polyvinylpyrrolidone, poly vinyl alcohol, hydroxymethylcellulose, hydroxypropylmethylcellulose, etc. The hydrophilic polymer may represent 20-60% by weight of the composition, and preferably 25 to 45% by weight. Thus, Stamm's formulations are well outside the claimed range of 2-15% by weight. As shown in more detail below, various filings associated with the Stamm patent teach away from the claimed invention by demonstrating improvement in fenofibrate bioavailability by increasing, not decreasing, the amount of binding cellulose derivative.

Stamm's hydrophilic polymer quantities are determined excluding an optional outer layer. To clarify that applicants' binding cellulose derivative is likewise determined exclusive of any such optional added layers, and thereby more clearly distinguish the claimed invention over the Stamm reference, applicants have amended claim 34 such that the binding cellulose derivative is measured relative to the combination of only the neutral core, and the fenofibrate, the surfactant, and the binding cellulose derivative of the active layer. As such, applicants restrict the claimed quantities of binding cellulose derivative by excluding from that calculation other agents and excipients, and the calculation is performed in a manner consistent with that in Stamm.

As discussed above, Stamm and its related applications and proceedings, teach away from the claimed invention by showing that increased binding cellulose derivative relative to fenofibrate improve bioavailability of fenofibrate.

Stamm '670 is the US equivalent of EP 0952829. Both claim priority to FR 9700479; and both are owned by Fournier, and relate to TRICOR® 160 mg. (LIPANTHYL® 160 mg is the tradename used for TRICOR® 160 mg in Europe; Annex 1 is from the website of SOLVAY PHARMACEUTICALS, which acquired Fournier in 2005.)

EP 09528829 was granted March 5, 2003. An opposition proceeding was instituted against this patent on December 5, 2003 by Ethypharm, the owner of the instant application. As a result of the opposition proceedings, the patent was amended but maintained. Ethypharm appealed that decision December 11, 2006.

On June 23, 2006, Fournier, through its counsel, Hirsch & Associes, filed papers in the European Patent Office in preparation of the oral proceedings held on July 3 and 4, 2006 (Annex 2). Excerpts of the papers are attached and include:

- Observations submitted with the letter of Hirsch & Associes, dated June 23, 2006 (pages 2 - 3);
- Table of prior art relative to EP '829;
- D1a (Boyer US 4,800,079);
- D44: page II-A-7 extracted from the file of LIPANTHYL® 160 mg for approval by the French Health Administration (The French "FDA");
- D46: a letter addressed to the French Health Administration, about LIPANTHYL® 200 and 67 mg.

Also enclosed is an English translation of the encircled passage of Section 4 of the Observations (Annex 3). That passage includes the statement: "In order to respond to the objection, the patentee provides data from his file for approval [to] the French Agency of Sanitary Security of Health Products (AFSSAPS):" The information is taken from the file for product approval for LIPANTHYL® 160 mg to the French equivalent of the FDA.

That passage refers to the dissolution results of three fenofibrate formulations: 18.66% PVP, 25.60% PVP, and 31.45% PVP. The lowest concentration of PVP is 18.66%. EP '829 does not teach or suggest pharmaceutical formulations including PVP concentrations within the presently claimed range.

Fournier describes D44 in its Table of Prior Art as a "Report on Dissolution (variation quantities of PVP)." It is taken from the application for regulatory approval of LIPANTHYL® 160 mg to the French equivalent of FDA. D44 also references three fenofibrate formulations varying in PVP concentration, but expresses relative cellulose concentration as fenofibrate/povidone, and lists them as: 2/1, 4/3, and 1/1. Although not expressly stated, it stands to reason that the 2/1 formulation corresponds to 18.66 % of PVP; the 4/3 formulation corresponds to 25.60% of PVP; and the 1/1 formulation corresponds to 31.45% of PVP as the data are taken from the application for regulatory approval of the same product.

From D44, we know that the percentage of PVP in LIPANTHYL® 160 mg (also TRICOR® 160 mg), is 18.66% or 25.60% or 31.45%. Although the publicly available information does not permit us to conclusively state which of those formulations is LIPANTHYL® 160 mg, it is of no moment. All three formulations contain a cellulose derivative concentration above the presently claimed range of 2-15%; and there has been no showing that Stamm teaches or suggests, explicitly or implicitly, formulations within the claimed range.

Moreover, the D44 document shows that Stamm teaches away from the presently claimed formulations. Stamm's formulae containing the greatest amount of PVP (31.45%) exhibited the best dissolution profile. Thus, the combined teachings of Fournier, including its regulatory filings and the Stamm references, show that the Fournier formulations (LIPANTHYL® [a.k.a. TRICOR®] 160 mg) improve the dissolution profile of fenofibrate by increasing PVP relative to fenofibrate. The relationship of fenofibrate to binding cellulose derivative in the Stamm/Fournier formulations is contrary to that found in Applicants' formulations. In Applicants' formulations the fenofibrate dissolution rate is improved by significantly reducing the relative concentration of binding cellulose derivative compared to the prior art.

In support of that proposition, Applicants submit herewith a Declaration of George Bobotas, as it was submitted in related U.S. Application Serial No. 10/030,262 (Annex 4). The Bobotas Declaration shows that the presently claimed formulations can improve the dissolution profile of fenofibrate by reducing the percentage of polymer and increasing the percentage of fenofibrate. Applicants' presently claimed formulations thus increase fenofibrate bioavailability which, in turn, permits a substantial reduction of fenofibrate dosage while providing the same therapeutic effect (*see, e.g.,* page 2, paragraph 4 of the Bobotas Declaration).

The Bobotas Declaration shows that, contrary to the teachings of Stamm, fenofibrate dissolution is enhanced in certain formulations by decreasing - rather than increasing - the relative concentration of cellulose derivative. Thus, the presently claimed invention would not have been obvious in view of Stamm, either alone or in combination with the other cited references.

Finally, Stamm fails to cure the deficiencies of either Boyer or Curtet, or any of the other cited references. As discussed above, Stamm teaches that to improve bioavailability of fenofibrate, the relative concentration of binding cellulose derivative should be increased from about 20% by weight. Neither Boyer nor Curtet have been shown to teach or suggest decreasing that amount. Accordingly, Stamm, taken alone or in combination with the other cited references, fails to teach or suggest the claimed invention.

The Remaining References

The remaining references also fail to cure the various deficiencies of the Curtet, Boyer, and/or Stamm. The pslgroup.com document is relied upon as teaching "administering a micronized from of the drug fenofibrate to a set population with high serum triglyceride and hyperlipidemia"; but "fails to teach how the pharmaceutical composition comprising fenofibrate was formed." Applicants acknowledge that micronized fenofibrate was known in the art, as was its use in treating high serum triglycerides and hyperlipidemia. However, it has not been shown that the reference teaches or suggests any other material elements of the claimed invention. Thus, there is no prima facie case of obviousness in combining the pslgroup.com reference with the other cited references. It is at best merely cumulative of the other references disclosing micronized fenofibrate.

Similarly, the HHS FDA CDER ("CDER") reference fails to cure the deficiencies of any of the other cited references. The CDER reference acknowledges the existence of the food effect in certain pharmaceuticals, and provides Guidance for Industry in designing and presenting "Food Effect Bioavailability and Bioequivalence Studies." Notably, the reference fails to teach how to eliminate the food effect, but instead focuses on how to identify it, assess it, and measure it, among other things. Further, the reference does not address the food effect in any particular active agent, and thus does not teach or suggest how it might be reduced or eliminated in the specific case of fenofibrate. Thus, the CDER reference fails to cure the deficiencies of the other cited references.

Munoz also fails to cure the deficiencies of the other references. Munoz is relied upon as showing that Lipanthyl 200 Micronized has reduced food effect relative to Lipanthyl 300 Micronized. However, there is no showing that the reported result would teach or suggest the claimed invention. Applicants acknowledge that workers in the field have been striving to enhance fenofibrate bioavailability and reduce or eliminate the food effect associated with its administration. The Munoz reference, however, seems to be nothing more than a report of the advantages of micronized fenofibrate. The existence of micronized fenofibrate in the prior art is recognized and admitted throughout applicants' specification. *E.g.,* ¶ **0008**.

Additionally, micronized fenofibrate is disclosed and used in several other cited references, e.g., Stamm and Boyer. There is no showing how the Munoz reference cures the deficiencies of any of the other references beyond the mere disclosure of micronized fenofibrate. As such it appears to be merely cumulative. Accordingly, the Munoz reference, alone or in combination with any of the other references, fails to teach or suggest the claimed invention.

Double Patenting

Applicants acknowledge the double patenting rejection, and upon indication of allowable subject matter, will submit a terminal disclaimer relative to USSN 11/509,806.

Conclusion

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: February 29, 2008

By:
Brian P. O'Shaughnessy
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P.O. Box 1404
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ANNEX 1

SOLVAY PHARMACEUTICALS

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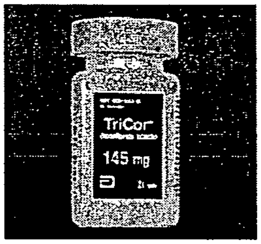
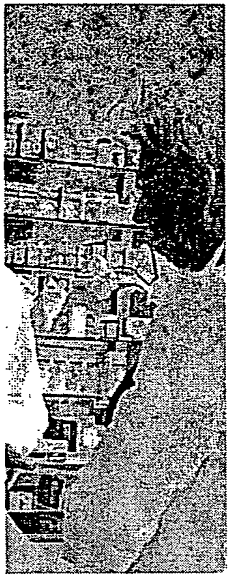


TRICOR® (Lipanthyl®) is a very successful fenofibrate which was added to our portfolio after the acquisition of Fournier Pharma. Therapeutic doses of TRICOR® produces elevation of the 'good' HDL cholesterol, a reduction in the content of the 'bad' LDL cholesterol, and a substantial reduction in triglycerides (major component of fat tissue). The active ingredient in fenofibrate is fenofibric acid. Fenofibric acid inhibits the synthesis of cholesterol as well as enhancing its elimination as bile salts, while in addition both inhibiting the synthesis of triglycerides and enhancing their breakdown. In the US, where fenofibrate is co-promoted under the brand name TRICOR® with Abbott, the product has become a blockbuster.

Four classes of drugs are commonly used to lower cholesterol: statins, fibrates, bile acid sequestrants and nicotinic acid. Statins have the highest market share, but there is an increasing tendency for combination therapy because one drug is often not enough to lower cholesterol to normal levels and combinations allow treatment more specifically suited to individual patients' needs.



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Date of last update: 16/8/2007

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ANNEX 2

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RUSH !
ORAL PROCEEDINGS
JULY 3 & 4 !

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ALLEMAGNE

Paris, le 23 Juin 2006

EPO - Munich
42
28. Juni 2006

FAX

CONFIRMATION

N/Réf.: 14198 EP LFS 1
FP/MG

Brevet Européen
n° 98900125.0 du 16/01/98
au nom de : - LABORATOIRES FOURNIER S.A.

Messieurs,

En vue de la procédure orale du 03 et 04 Juillet 2006, vous trouverez ci-joint :

- des observations
- des nouveaux documents

Une copie des présentes est envoyée aux opposants à titre confracternel.

Nous vous prions d'agréer, Messieurs, l'expression de nos salutations distinguées.

François Pochart
Groupement 161

Copie :
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OBSERVATIONS EN VUE DE LA PROCEDURE ORALE DES 3 ET 4 JUILLET 2006 OPPOSITION FORMEE A L'ENCONTRE DU BREVET EP-B-0952829

Pour la procédure orale à venir, le breveté souhaite répondre ce qui suit.

1). Personnes présentes.

Le mandataire, François Pochart, sera accompagné des personnes suivantes (étant entendu que l'exposé des faits, preuves et arguments sera effectué par le mandataire).

- Pierre Diebolt, mandataire européen et salarié du breveté;
- Aude Gruber, ingénieur brevet débutante et salariée du breveté, agissant pour la procédure comme assistante du mandataire;
- Philippe Hubert, mandataire européen;
- Bruno Racheboeuf, salarié du breveté et porteur d'un pouvoir;
- Martin Gosmann, mandataire européen.

2). Nouveaux motifs.

L'opposant SMB, intervenant a soulevé le motif 100(c) ensemble 123(2) pour la première fois il y a seulement un mois. Le breveté ne peut pas s'opposer à l'examen d'un nouveau motif d'opposition lors d'une intervention, mais encore faut-il que ces motifs soient soulevés au moment de l'intervention. Mais le motif sous 123(2) n'a été soulevé que tardivement, après le délai de l'intervention; en outre il n'est manifestement pas applicable à aucune des requêtes en instance, puisque ces requêtes ne font que combiner des revendications dépendantes.

Si la Division d'Opposition devait considérer ce motif proprio motu, en application de G9/91 et G10/91, le breveté souhaite rappeler les limites de la saisine d'office d'une division d'opposition.

> *"Ainsi, une division d'opposition peut, en application de l'article 114(1) CBE, soulever d'office un motif d'opposition qui ne soit pas couvert par la déclaration visée à la règle 55c) CBE, ou examiner un motif invoqué par l'opposant (ou mentionné par un tiers en vertu de l'article 115 CBE) après l'expiration du délai prévu à l'article 99 (1) CBE. Parallèlement, la Grande Chambre tient à souligner qu'il ne devrait être procédé devant la division d'opposition à l'examen de motifs qui ne sont pas réellement compris dans la déclaration selon la règle 55c) CBE, à titre d'exception au principe établi par la Chambre au point 6 ci-avant, que dans des affaires où, de prime abord, il existe de solides raisons de croire que ces motifs sont pertinents et qu'ils s'opposeraient en totalité ou en partie au maintien du brevet européen." (G9/91, motifs)*
>
> *"A titre exceptionnel, la division d'opposition peut, en application de l'article 114(1) CBE, examiner d'autres motifs d'opposition qui, de prime abord, semblent en tout ou partie s'opposer au maintien du brevet européen. (G10/91, sommaire)"*

Les conditions "de prime abord" ne sont manifestement pas remplies en l'espèce.

Si ce motif devait être invoqué, le breveté se réserve la possibilité de présenter de nouvelles requêtes visant à répondre à ce nouveau motif. Dans la mesure où ce motif est manifestement tardif, le breveté doit être en mesure de répondre, et ce jusque pendant la procédure orale.

3). Documents tardifs.

Tant Ethypharm que SMB ont produit de nouveaux documents et résultats de tests. Le breveté rappelle que dans sa réponse de Novembre 2005 il avait demandé des précisions quant aux conditions expérimentales, et que celles-ci n'ont été fournies que très tardivement. Le breveté est donc placé dans une situation difficile, n'ayant pas le temps de préparer de contre-expertise.

Les documents cités ne sont pas plus pertinents que ceux déjà cités et sont donc tardifs pareillement.

Ces documents doivent donc être écartés.

4). Nouveaux documents.

Le breveté dépose ce jour de nouveaux documents, qui visent à répondre aux objections soulevées par les opposants tardivement, et notamment en ce qui concerne les tests. Dans la mesure où le breveté dispose d'un dispositif Glatt, mais dans une usine, que cette usine est dite GMP, et que la modification d'un processus GMP implique des modifications et des contrôles très stricts, il a été impossible pour le breveté de reproduire les tests fournis par les opposants.

Pour répondre à l'objection, le breveté fournit des éléments tirés de son dossier d'homologation devant l'agence française de sécurité sanitaire des produits de santé (Afssaps):

- résultats de dissolution pour une variation de la quantité de PVP dans un comprimé (la quantité peut être rapportée par homothétie à celle de l'exemple du brevet), ce qui correspond aux pourcentages suivants 18,66%, 25,60% et 31,45%;
- résultats de dissolution pour des compositions selon l'invention et selon l'état de la technique (précédent produit du breveté), granulé ou comprimé;

=) See ANNEX 3 for English Translation

Par ailleurs, pour répondre à l'objection relative aux modifications de l'autorisation de mise sur le marché, le breveté verse aux débats ses échanges avec l'autorité sanitaire. (Le fait que le numéro de l'autorisation administrative n'ait pas été modifié ne signifie en rien que le contenu de celle-ci n'a pas changé.) Le breveté précise en outre que le dictionnaire Vidal est édité par une société privée qui n'a aucun lien avec l'Afssaps.

Enfin, le breveté dépose un document D1a, qui n'est que le correspondant US-P-4800079 du document D1. D1a décrit clairement dans sa revendication 1 que la technologie est une forme retard ou prolongée ("*granules with controlled release of fenofibrate*"), et non à libération immédiate. Ce document est motivé par l'argument que D1 est considéré par les opposants et intervenants comme décrivant une libération immédiate. Ce document n'étant que le correspondant américain de D1, il doit être admis dans la présente procédure et n'est pas tardif. Le contenu technique de ce document est réputé être identique à celui de D1.

5). Liste de documents.

Le breveté a préparé un listing avec une numérotation des documents qu'il propose de suivre pour la procédure orale à des fins de simplicité, la numérotation commençant comme indiqué par la Division d'Opposition dans son opinion préliminaire.

	Ethypharm	SMB	Fournier	Documents
D1	E1			EP 0 256 933 A
D1a			D1a	US 4800079
D2	E2			EP 0 519 144 A
D3	E3			EP 0 330 532 A
D4	E4			WO 82/01 649 A
D5	E5			WO 96/01 621 A
D6	E6			US 4,412,986 A
D7	E7			EP 0 761 208 A
D8	E8			D.F Temeljotov et al. Acta Pharm. 1996, 131-136
D9	E9			EP 0 793 958 A
D10	E10			FR 2 758 459 A
D11	E11			Handbook of pharmaceutical excipients, 1994, 392 (Povidone)
D12		S2		WO 96/21 439
D13		S4		Dissolution du Lipanthyl 200mg
D14		S7		Rapport Amighi
D15		S5		A New Formulation of Fenofibrate : Suprabioavailable Tablets
D16		S1		Requête en saisie description du 16.12.2004
D17a		S3		Conclusions de Fournier du 07.03.2005
D17b			S3a	Conclusions de Fournier du 7.3.2005
D18		S8		Citation (procédure en déclaration de non contrefaçon
D19	E12			EP 0 012 523
D20	E13			Kuchiki A., et al., Yakuzaigaku 44(1), 1984, 31-7
D21	E14			Pharmaceutical pelletization technology, Ed. Ghebre-Sellassie, I. 1989, Ch. 7 and 10
D22			D14a	Pharmaceutical pelletization technology, Ed. Ghebre-Sellassie, I. 1989, Ch. 1
D23				WO 03/013 500
D24	E24			US 4 717 569
D25	E25			Handbook of pharm excipients, 1994, 143-144 (Crospovidone)
D26	E26			Plainte devant la cour de Delaware du 01.06.04
D27a	E27			Mode de préparation des granulés de fénofibrate selon EP 952 829 (exemple 1)
D27b	E27			Analyse de différents lots de Lipanthyl par Ethypharm
D27c	E27			Note technique du Professeur Rosset
D28	E28			US 6 074 670
D29	E29			US 6 277 405 (correspondant au brevet opposé)
D30	E30			Extrait des Vidal 1995(a), 1999(b), 2001(c) et 2004(d)
D31	E31			US 5 145 684
D32	E32			Réalisation d'une compositionà bvase de fénofibrate micronisé et de polymère hydrophile selon EP 952 829
D33	E33			Handbook of pharm. excipients (1994), 71-73 (Carbomer)
D34		D24		FR 2 722 984
D35		D25		Reason for order – procédure au Canada
D36		D26		CA 2 219 475
D37		D27		Jugement en Allemagne + sa traduction anglaise
D38		D28		Déclaration Marianne Starnikov
D39		D29		Tests de bioéquivalence
D40		D30		Appareil de mesure « Coulter Counter ».
D41		D31		Merck Index - Lactose

D42		D32		Rapport de tests
D43		D33		Document commercial sur les Plasdone® Povidone.
D44			D44	Rapport sur dissolution (variation quantité PVP)
D45			D45	Rapport sur dissolution (invention/état de la technique)
D46			D46	Lettre Afssaps

D1a

United States Patent [19]
Boyer

[11] **Patent Number:** 4,800,079
[45] **Date of Patent:** Jan. 24, 1989

[54] MEDICINE BASED ON FENOFIBRATE, AND A METHOD OF PREPARING IT

[76] Inventor: Jean-François Boyer, 73 rue des Jeux de Billes, 78550 Houdan, France

[21] Appl. No.: 83,409
[22] Filed: Aug. 10, 1987
[51] Int. Cl.^{4} A61K 9/14
[52] U.S. Cl. 424/482; 424/490
[58] Field of Search 424/482, 490

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,672,945 6/1972 Taylor .... 428/404 X
4,191,741 3/1980 Hudson et al. .... 424/425 X
4,261,971 4/1981 Applegren et al. .... 424/494 X
4,615,697 10/1986 Robinson .... 424/491 X
4,721,619 1/1988 Panoz et al. 424/459

Primary Examiner—William R. Dixon, Jr.
Assistant Examiner—Andrew Griffis
Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak & Seas

[57] **ABSTRACT**

A granular medicine based on fenofibrate, each granule comprising an inert core, a layer based on fenofibrate, and a protective layer, the medicine being characterized in that the fenofibrate in the layer based on fenofibrate is present in the form of crystalline microparticles of dimensions not greater than 30 microns, and preferably less than 10 microns.

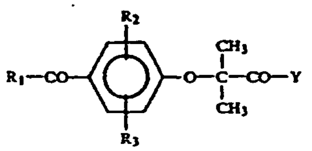
7 Claims, No Drawings

MEDICINE BASED ON FENOFIBRATE, AND A METHOD OF PREPARING IT

The present invention relates to a medicine based on fenofibrate, and also to a method of preparing it.

BACKGROUND OF THE INVENTION

It is recalled that fenofibrate is isopropyl para-(4-chlorobenzoyl)-pehnoxyisobutyrate. In the present application, the term "fenofibrate and its derivatives" is used to designate compounds having formula I:



(I)

in which:

R_1 represents a phenyl group or a phenyl group substituted by one or more —CH_3, CF_3 or by halogens (in particular fluorine, chlorine, or bromine);

R_2 and R_3 independently represent a hydrogen atom or a halogen atom (preferably fluorine, chlorine, or bromine), an alkyl or an alkoxy group having 1 to 5C or one of the following groups: —CF_3, —SCH_3, —$SOCH_3$, —SO_2CH_3, or —OH; and

Y represents one of the following groups: —OH; inferior alkoxy, preferably in C_1–C_4; —NR_4R_5; —$NHCH_2CH_2NR_4R_5$; or —O-alkylene-NR_4R_5, with the alkylene having, in particular, two to six atoms of carbon, and with R_4 and R_5 being identical or different and each representing a hydrogen atom or one of the following groups: C_1–C_5 alkyl, C_3–C_7 and preferably C_5–C_6 cycloalkyl; aryl or aryl substituted on the aromatic residue by one or more halogen, methyl, or —CF_3 groups; or else R_4 and R_5 constitute, together with the nitrogen atom to which they are connected, one fo the following groups: either an n-heterocyclic group having 5 to 7 vertices capable of enclosing a second hetero-atom selected from N, O, and S, and capable of being substituted; or else an amide residue derived from lysine or cysteine.

Naturally, the expression "fenofibrate and its derivatives" also covers the salts that can be obtained from compounds of formula I by adding pharmaceutically acceptable acids.

Fenofibrate is used in the treatment of adult endogenous hyperlipidaemia, hypercholesterolaemia, and hypertrigylceridaemia. Thus, in an adult being treated with 300 to 400 mg per day of fenofibrate, there can be observed a 20% to 25% reduction in chlolesterolaemia and a 40% to 50% reduction in triglyceridaemia.

The unaltered substance is not found in plasma. The major plasmatic metabolite is fenofibric acid.

On average, the maximum concentration in plasma is reached five hours after taking the medicine. The average concentration in plasma is about 50 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout continuous treatment.

Fenofibric acid is strongly bound to plasmatic albumin and can displace antivitamins K from protein fixing sites and potentialize their anticoagulant effect.

The half-life for eliminating fenofibric acid from plasma is about twenty hours.

Under these conditions, it will be understood that there is no need to take it more than once a day.

It has been observed that fenofibrate has poor solubility in aqueous liquids, thereby giving rise to non-uniform absorption in the digestive tube, and in accordance with the present invention a galenical preparation has been devised which considerably improves absorption by the digestive tube.

SUMMARY OF THE INVENTION

The present invention provides a medicine based on fenofibrate and in the form of granules, each granule comprising an inert core, a layer based on fenofibrate, and a protective layer. In the layer based on fenofibrate, the fenofibrate is present in the form of crystalline microparticles of dimensions not greater than 30 microns, and preferably less than 10 microns.

In accordance with the present invention, this structure is obtained by a method including a step of projecting a damp and sticky outer layer onto the inert cores, followed by a step of projecting fenofibrate microparticles onto the damp layer with the dampness being rapidly evaporated in order to prevent it from dissolving the fenofibrate microparticles while never-the-less fixing said fenofibrate microparticles onto the cores, with said two steps being repeated until a sufficient quantity of fenofibrate has been fixed onto the cores.

The damp and sticky layer may advantageously be constituted by a solution of a polymer in alcohol or by an aqueous suspension of the polymer, and the alcohol solution may be prepared using alcohols which are commonly used in pharmacology.

MORE DETAILED DESCRIPTION

There follows a description, by way of example, of the manufacture of one embodiment of a medicine in accordance with the present invention.

Inert grains for forming the inert cores are prepared in conventional manner. For example, each grain may be a sucrose crystal having a diameter of 0.3 mm. A suspension of maize starch is sprayed onto the crystals, the suspension comprising 27% by weight of maize starch in a hot sugar solution (prepared, for example, by dissolving 73 kg of sugar in 32 kg of water: 27 kg starch, 73 kg sugar, 32 kg water). The sugar solution is projected at 50° C. into a turbine which is itself heated to 50° C. The quantity projected is adjusted so that the diameter of each grain increases from 0.3 mm to 0.6 mm, with the grain having about 25% by weight starch and about 75% sucrose, once the water has evaporated from the sugar solution.

Thereafter, the inert cores are rotated in a turbine and they are dampened with an alcohol solution containing 12.5% by weight of a methylacrylic polymer (95° alcohol). The grains become damp and sticky. Fenofibrate powder is then projected onto them, with the powder being obtained by crushing fenofibrate crystals until microparticles are obtained. A typical powder has the following partical size distribution:

100%<30 microns
99.5%<20 microns
98%<10 microns
88%<5 microns.

The grains are then immediately dried very rapidly in order to prevent the alcohol from having enough time to dissolve the fenofibrate (a flow of air is passed through the turbine). This avoids destroying the microparticulate structure which offers a considerable area for encouraging absorption. A single thickness of microparticles is thus deposited on the sticky grain where the microcapsules are fixed by adherence. The operations of dampening-projecting-drying may be performed in about one or two minutes. These operations of dampening the core and projecting microparticles are repeated until all of the powder has been incorporated.

Finally, a protective coating is applied, e.g. a thin layer of methacrylic polymer, representing about 1% by weight of each granule.

Granules obtained in this way are put into capsules, with a dose of 250 mg of fenofibrate per capsule.

The fenofibrate layer structure is similar to that of a sponge, with the pores containing microparticles of fenofibrate. The sponge is constituted by a binder which is soluble in an aqueous medium: methacrylate or polyvinylpyrolidone. Once the binder has dissolved, the microparticles of fenofibrate are released and can prevent their entire areas to the process of absorption in the intestinal aqueous medium.

One example of formulation is as follows:

fenofibrate	400 kg
inert grains	110 kg (sugar and/or starch)
polyvinylpyrolidone and/or methacrylate	20 kg

Of the last 20 kg, about 5 kg are used for making the protective envelope (about 1% of the total weight) and the remainder (about 15 kg) is used for binding the microparticles of fenofibrate, with alcohol being used temporarily as the solvent.

The quantity of binder is determined so that at least 65% of the fenofibrate is released in one hour in a water based liquid medium.

This fraction can be measured as follows: the contents of a capsule is placed in a flask containing 35 ml of a medium having a pH of 1.5. The flask is stirred at 30 rpm and at 37° C. After stirring for one hour, the percentage of fenofibrate that has been released from the galenical preparation in accordance with the invention is greater than 65%.

Composition of the medium:

118 ml normal hydrochloric acid

84 ml solution of normal sodium hydroxide distilled water: enough to obtain 1000.0 ml of medium.

The pH of the medium lies between 1.45 and 1.55.

Medicines in accordance with the invention have also shown reductions in variability of blood concentrations both inter and intra patient (i.e. on the same patient or between different patients).

I claim:

1. Medicine in the form of granules with controlled release of fenofibrate, each granule comprising an inert core, a layer based on fenofibrate and a protective layer, wherein the improvement comprises the layer based on fenofibrate containing the fenofibrate in the form of crystalline microparticles of dimensions not greater than 30 microns, said microparticles being included in the pores of an inert matrix soluble in water.

2. A medicine according to claim 1, wherein the inert matrix is composed by a binder selected from the group comprising: methacrylic polymers, polyvinylpyrolidone, mixtures thereof; cellulose derivatives; and polyethylene glycols.

3. A medicine according to claim 1, wherein the inert core has a diameter of about 0.3 mm to about 0.6 mm and is constituted by a substance selected from the group comprising: glucose, sucrose, lactose, and their equivalents, and starch, and mixtures thereof.

4. A medicine according to claim 1, wherein the protective layer represents about 1% by weight of each granule, and is formed of a substance selected from the group comprising: methacrylic polymers, polyvinylpyrolidone, mixtures thereof; cellulose derivatives; and polyethylene glycols.

5. A medicine according to claim 1, wherein the quantity of binder is such that the quantity of fenofibrate liberated in one hour in an aqueous liquid is not less than 65%.

6. Medicine according to claim 1 wherein the dimensions of said microparticles are less than 10 microns.

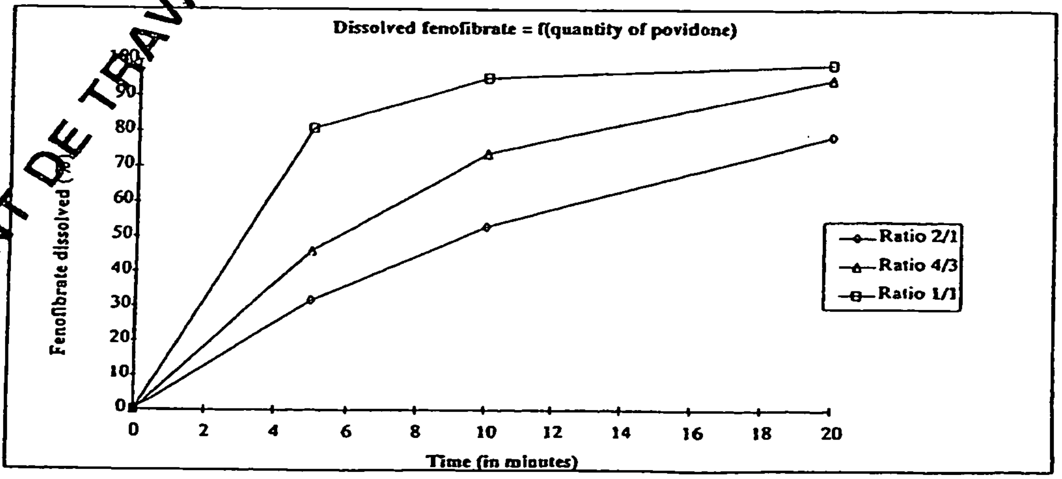
7. Medicine according to claim 3 wherein the starch is maize starch.

* * * * *

D.44

Three formulations with fenofibrate/povidone K25 ratio of 2/1 - 4/3 and 1/1 were manufactured and a dissolution test was performed. The results show that dissolution is fast and complete for the formula containing a ratio fenofibrate/povidone equal to 1. For the formulae presenting a ratio fenofibrate/povidone less than 1, the dissolution is slowed down.

Time (in minutes)	Fenofibrate/povidone K25 ratio		
	2/1	4/3	1/1
	Fenofibrate dissolved (%)	Fenofibrate dissolved (%)	Fenofibrate dissolved (%)
0	0	0	0
5	31.6 ± 4.4	46.2 ± 1.8	81.0 ± 2.0
10	53.2 ± 4.4	73.9 ± 4.6	95.1 ± 1.4
20	78.9 ± 2.9	94.9 ± 7.0	99.2 ± 0.2



DOCUMENT DE TRAVAIL PROPRIETE DES LABORAT

FRANCE : LIPANTHYL 67 - LIPANTHYL 200

AGENCE
DU
MEDICAMENT

DIRECTION DE L'EVALUATION
UNITÉ PHARMACEUTIQUE "CHIMIE"

RÉPUBLIQUE FRANÇAISE

SAINT-DENIS, le 08 FEV. 1999

143-147 boulevard Anatole France
93285 SAINT-DENIS CEDEX
Tél 01 55 87 33 81
Fax 01 55 87 33 82

Monsieur le Titulaire de
l'Autorisation de Mise sur le Marché
Laboratoires FOURNIER S.A.
9 rue du Petitot
21000 DIJON

D46

Dossier suivi par : Mme Sophie LALAUDE

Réf. à rappeler : NL 17741 - NL 16385
GTPh n° 401
SL/AS/CB

Monsieur,

Par les courriers du 03 novembre 1998, du 10 novembre 1998 et du 24 novembre 1998 relatifs aux spécialités :

- LIPANTHYL 67 MICRONISE, gélule
- LIPANTHYL 200 MICRONISE, gélule

vous avez souhaité :

- modifier le procédé de fabrication du produit fini ;
- l'agrément d'un quatrième producteur de principe actif :

Une suite favorable a été réservée à votre demande.

Veuillez agréer, Monsieur, l'expression de ma considération distinguée.

Pour le Directeur Général
et par délégation

l'Adjoint au Directeur de l'Evaluation
Chargé des Affaires Médicales
Dr F. MEYER

C:\GRP_PHCH\MODIF\LABO\1998\NL17741.L2

D45

DOCUMENT DE TRAVAIL P

Table 1 II-A: **Dissolution profiles of capsules (200 mg fenofibrate) and tablets (160 mg fenofibrate)**

Time in minutes	Tablets (% of dissolved fenofibrate)		Capsules (% of dissolved fenofibrate)	
	Batch 197-6 0.1M LSNa	Batch 197-6 0.025M LSNa	Batch 49 0.1 M LSNa	Batch 49 0.025M LSNa
0	0	0	0	0
10	89	65	26	10
20	101	88	76	47
30	101	94	88	63
40	101	96	93	71
50			96	76
60	100	98	98	80
120			103	88

3

ANNEX 3

In order to respond to the objection, the patentee provides data from his file for approval the French Agency of Sanitary Security of Health products (AFSSAPS):

- Dissolution results depending on the amount of PVP in a tablet (the amount is in a homothetic ratio to the example of the patent), which corresponds to the following percentage: 18.66 %, 25.60 % and 31.45 %;
- Dissolution results for compositions according to the invention and according to prior art (previous product from the patentee), granule or tablet.

4

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Bruno CRIERE et al.	Atty. Dck. No. 017751-030
Serial No.: 10/030,262	Group Art Unit: 1615
Filed: April 17, 2002	Examiner: Channavajjala, Lakshi Sarada

For: PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, George Bobotas, Ph.D., hereby declare and affirm that:

1. I am employed as Vice President, Scientific Affairs at Reliant Pharmaceuticals, Inc., the exclusive licensee of the above-identified patent application.
2. I have over 25 years of clinical and scientific affairs experience with leading pharmaceutical and clinical development organizations. I have extensive research experience and am a member of numerous professional organizations, including the American Association for the Advancement of Science, the New York Academy of Science, and the American Chemical Society. I previously worked as the Executive Director, CNS Center for Covance Inc., where I managed the operational, scientific, and financial aspects of the Center. Prior to Covance, I led Scientific Affairs and Licensing for Somerset Pharmaceuticals, Inc., New Product Licensing and Evaluation for Mylan Laboratories Inc., and

biochemistry and pharmacokinetics for Forest Laboratories, Inc. In addition, I am a listed inventor on five issued U.S. Patents and numerous U.S. patent applications. I hold a Doctorate in Biochemistry from City University of New York and Masters Degrees in Biochemistry from the City University of New York and in Physical Chemistry from Smith College.

3. I am submitting this Declaration in support of the referenced patent application. I am familiar with the subject matter described and claimed in the application. I am also familiar with U.S. Patent No. 4,895,726 ("the '726 patent") and U.S. Patent No. 6,074,670 ("the '670 patent").

Comparison Of Formulations Covered By The Present Invention To Commercial Embodiments Of The '726 Patent And The '670 Patent

4. I designed and supervised the performance of a comparison between pharmaceutical formulations covered by the present invention and commercial embodiments of the '726 and '670 patents. Several sets of comparative data are presented in this Section (Studies A, B and C). The data show that, with a healthy low-fat diet, on a per-milligram basis, fenofibrate formulations according to the present invention are more bioavailable than the commercial fenofibrate formulations covered by the '726 patent and/or the '670 patent. The data also show that by increasing the percentage of fenofibrate and reducing the percentage of polymer (in comparison to the amounts disclosed in the '670 patent), we can achieve a substantial increase in fenofibrate bioavailability, which, in turn, permits a substantial reduction in fenofibrate dosage while providing the same therapeutic effect.

Study A

5. *Study Design* – A randomized, single-dose, crossover study to assess the

relative bioavailability of 130 mg ANTARA® fenofibrate capsules[1] versus 200 mg TRICOR® fenofibrate capsules[2] in healthy adult subjects following consumption of a therapeutic lifestyle change (TLC) meal. 29 healthy adult males and females completed the study. Following randomization, subjects received a single dose of medication at the beginning of each treatment period. After completion of the first period, subjects crossed over. A washout period of at least 14 days occurred between treatment periods. Blood samples for the determination of plasma fenofibric acid were drawn prior to dosing and periodically up to 168 hours after dosing.

6. *Pharmacokinetic Results* – The following TABLE 1 summarizes selected pharmacokinetic parameters for fenofibric acid following a TLC meal (arithmetic mean (± SD)) and the ratios of least square means for 1n-transformed data (with 90% confidence intervals):

TABLE 1

Parameter	Treatment A: 130 mg ANTARA® capsules	Treatment B: 200 mg TRICOR® capsules	Ratio of LSM A/B% (90% CI)
$AUC_{0-\infty}$ (ng·h/ml)	132,387 (±40,251)	162,332 (±45,509)	83.2 (75.9-91.3)
C_{max} (ng/ml)	7,565 (±1,593)	7,554 (±2,934)	105.7 (90.5-123.5)
T_{max} (h)	4.21 (±0.632)	4.58 (±0.508)	N/A

7. The following TABLE 2 compares the relative bioavailability of the 130 mg fenofibrate formulation covered by the present invention, versus the 200 mg TRICOR® capsules covered by the '726 patent, on a per-milligram basis by

---

[1] This product, distributed by Reliant Pharmaceuticals, Inc., is covered by the present invention. The exact formulation of ANTARA® is a trade secret.

[2] Abbott Laboratories, Inc., the distributor of 200 mg TRICOR® fenofibrate capsules, listed the '726 patent in the Food and Drug Administration's "Approved Drug Products With Therapeutic Equivalence Evaluations" (also known as the "Orange Book") as covering the product.

comparing $AUC_{0-\infty}$:

TABLE 2

Treatment	Mean $AUC_{0-\infty}$	Mean $AUC_{0-\infty}$ per mg fenofibrate	% increase in bioavailability per mg
130 mg ANTARA® capsules	132,387	1,018	25.5%
200 mg TRICOR® capsules	162,332	811	

8. *Conclusions* – This single dose study compared the bioavailability of 130 mg ANTARA® fenofibrate capsules covered by the present invention, versus 200 mg TRICOR® fenofibrate capsules covered by the '726 patent, in subjects following consumption of a TLC meal. The formulation according to the present invention (130 mg ANTARA® capsules) showed a 25.5% increase in bioavailability on a per-milligram basis, as compared to the formulation covered by the '726 patent (200 mg TRICOR® capsules).

Study B

9. *Study Design* – A randomized, multiple-dose, crossover study to assess the relative bioavailability of 130 mg ANTARA® fenofibrate capsules versus 200 mg TRICOR® fenofibrate capsules at steady state in healthy adult subjects on a therapeutic lifestyle change (TLC) diet. 26 healthy adult males and females completed the study. Following randomization, subjects received a single dose of medication daily for 7 days. After completion of the first period, subjects crossed over to the alternate treatment for 7 days. A washout period of at least 14 days occurred between treatment periods. Blood samples for the determination of plasma fenofibric acid were drawn on day 1 prior to the first dosing and at steady state on day 7 of each treatment period, just prior to

administration of the final dose of the study drug (time 0) and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours postdose. Trough blood samples were taken on days 4, 5, 6, 7 and 8 of each treatment period to establish whether steady state had been reached.

10. *Pharmacokinetic Results* – The following TABLE 3 summarizes selected pharmacokinetic parameters for fenofibric acid at steady state following a TLC meal (arithmetic mean (± SD)) and the ratios of least square means for 1n-transformed data (with 90% confidence intervals):

TABLE 3

Parameter	Treatment A: 130 mg ANTARA® capsules	Treatment B: 200 mg TRICOR® capsules	Ratio of LSM A/B% (90% CI)
$AUC_{T,ss}$ (ng·h/ml)	182,889 (±53,669)	204,988 (±50,945)	88.4 (84.0-93.0)
$C_{max,ss}$ (ng/ml)	12,664 (±2,685)	13,810 (±2,781)	91.7 (85.1-98.7)
$T_{max,ss}$ (h)	4.89 (±0.978)	5.34 (±1.281)	N/A

11. The following TABLE 4 compares the relative bioavailability of the 130 mg fenofibrate formulation covered by the present invention, versus the 200 mg TRICOR® capsules covered by the '726 patent, on a per-milligram basis by comparing $AUC_{T,ss}$:

TABLE 4

Treatment	Mean $AUC_{T,ss}$	Mean $AUC_{T,ss}$ per mg fenofibrate	% increase in bioavailability per mg
130 mg ANTARA® capsules	182,889	1,406	37.3%

200 mg TRICOR® capsules	204,988	1,024	

12. *Conclusions* – This multiple-dose study compared the bioavailability of 130 mg ANTARA® fenofibrate capsules covered by the present invention, versus 200 mg TRICOR® fenofibrate capsules covered by the '726 patent, at steady state in subjects on a TLC diet. The formulation according to the present invention (130 mg ANTARA® capsules) showed a 37.3% increase in bioavailability on a per-milligram basis, as compared to the formulation covered by the '726 patent (200 mg TRICOR® capsules).

Study C

13. *Study Design* – A randomized, single-dose, crossover study to assess the relative bioavailability of 120 mg and 144 mg fenofibrate capsules covered by the present invention, versus 160 mg TRICOR® fenofibrate tablets[3] in healthy adult subjects following consumption of a National Cholesterol Education Program (NCEP) Step 1 low-fat diet. 15 healthy adult males completed the study. Following randomization, subjects received a single dose of medication at the beginning of each treatment period. After completion of each period, subjects crossed over. A washout period of at least 7 days occurred between treatment periods. Blood samples for the determination of plasma fenofibric acid were drawn prior to dosing and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours after dosing.

14. *Pharmacokinetic Results* – The following TABLE 5 summarizes selected pharmacokinetic parameters for fenofibric acid following a NCEP Step 1 low-fat

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[3] Abbott Laboratories, Inc., the distributor of 160 mg TRICOR® fenofibrate tablets, listed the '670 patent in the FDA's Orange Book as covering the product. (The '726 patent is also listed; however, the '726 patent claims only cover capsules, not tablets, and therefore the '726 patent is not relevant to this product.)

diet (arithmetic mean (± SD)) and the ratios of least square means for 1n-transformed data (with 90% confidence intervals):

TABLE 5

Parameter	Treatment A: 120 mg fenofibrate capsules	Treatment B: 144 mg fenofibrate capsules	Treatment C: 160 mg TRICOR® tablets	Ratio of LSM A/C% (90% CI)	Ratio of LSM B/C% (90% CI)
$AUC_{0-\infty}$ (ng·h/ml)	115,452 (±18,889)	132,467 (±22,929)	128,305 (±30,672)	91.6 (86.8-96.7)	105.1 (99.6-110.8)
C_{max} (ng/ml)	7,669 (±1,234)	8,750 (±1387)	6,708 (±1,488)	115.1 (104.1-127.2)	131.3 (118.8-145.1)
T_{max} (h)	4.07 (±0.863)	4.30 (±0.702)	3.93 (±0.728)	N/A	N/A

15. The following TABLE 6 compares the relative bioavailability of the 120 mg and 144 mg fenofibrate formulations covered by the present invention, versus the 160 mg TRICOR® tablets covered by the '670 patent, on a per-milligram basis by comparing $AUC_{0-\infty}$:

TABLE 6

Treatment	Mean $AUC_{0-\infty}$	Mean $AUC_{0-\infty}$ per mg fenofibrate	% increase in bioavailability per mg
120 mg fenofibrate capsules	115,452	962	20.0%
144 mg fenofibrate capsules	132,467	920	14.7%
160 mg TRICOR® tablets	128,305	802	

16. *Conclusions* – This single dose study compared the bioavailability of 120 mg and 144 mg fenofibrate capsules covered by the present invention, versus 160 mg TRICOR® fenofibrate tablets covered by the '670 patent, in subjects following consumption of a NCEP Step 1 low-fat diet. The formulations according to the present invention (120 mg and 144 mg capsules) showed a 20.0% and 14.7% increase, respectively, in bioavailability on a per-milligram basis, as compared to the formulation covered by the '670 patent (160 mg TRICOR® tablets).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent(s) issuing therefrom.

Date: 10/21/05

George Bobotas
George Bobotas

List of Attachments

A. Product Insert Lipidil®

B. Product insert Tricor® (67, 134 & 200 mg)

C. 2002 Orange Book listing for Tricor®

D. Product insert Tricor® (54 mg and 160 mg)

E. Product insert for Tricor® (48 & 145 mg)

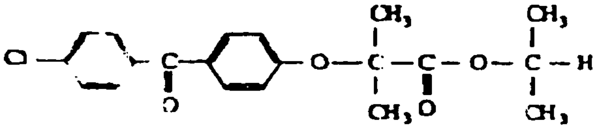
F. Product insert for Antara®

A

LIPIDIL®
(Fenofibrate Capsules)

DESCRIPTION

LIPIDIL (fenofibrate capsules) is a lipid regulating agent. It is available as capsules for oral administration. Each capsule contains 100 mg of fenofibrate. Each capsule also contains lactose, NF, magnesium stearate, NF, and pregelatinized starch, NF. The chemical name is 2-(4-(4-chlorobenzoyl phenoxy)-2-methylpropanoic acid, 1 methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}ClO_4$ and the molecular weight is 360.84; fenofibrate is insoluble in water. The melting point is 77-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

CLINICAL PHARMACOLOGY

The effects of LIPIDIL 100 mg tid on serum triglycerides were studied in two randomized, double-blind clinical trials[1]. 147 hypertriglyceridemic patients (Types IV and V) were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 250 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with LIPIDIL decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol as seen in the following table of changes seen at the end of treatment in patients with triglycerides of 500 to 1500 mg/dL.

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Changes in Lipid and Lipoprotein Determinations. Type IV/V Patients

	Placebo		LIPIDIL (100 mg tid)		
	Baseline Mean (mg/dL)	% Change	Baseline Mean (mg/dL)	% Change	Net Difference (of %)
Triglycerides					
Total	[illegible]	+ 7	726	- 55	- 62
VLDL	[illegible]	+ 19	543	[illegible]1	- 70
Cholesterol					
Total	[illegible]	0	261	14	- 14
HDL	[illegible]	+ 5	30	- 23	+ 18
LDL	10[illegible]	- 4	103	+ 45	+ 49
VLDL	[illegible]	+ 11	126	- 49	- 60

The mechanism of action of LIPIDIL has not been clearly established in man. Fenofibric acid, the active metabolite of fenofibrate, lowers plasma triglycerides apparently by inhibiting triglyceride synthesis, resulting in a reduction of VLDL released into the circulation, and also by stimulating the catabolism of triglyceride-rich lipoprotein (i.e., VLDL). LIPIDIL also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single radiolabelled 300 mg dose of fenofibrate appeared in the urine primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration, and the compound is eliminated with a half-life of 20 hours. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with 100 mg/day, and did not demonstrate accumulation across time following multiple dose administration. In elderly volunteers 77-87 years of age, the oral clearance of fenofibric acid following a single oral dose of 100 mg was 1.2 L/h, which compares with 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

In a study in patients with severe renal impairment (creatinine clearance < 50 ml/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage

However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 ml/min) the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults. Therefore, the dosage of LIPIDIL should be reduced in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

INDICATIONS AND USAGE

LIPIDIL (fenofibrate capsules) is indicated as adjunctive therapy to diet for treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who are at risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dL and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dL are unlikely to present a risk of pancreatitis. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention. LIPIDIL therapy may be considered for these subjects with triglyceride elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of LIPIDIL therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

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Because the benefit/risk ratio of LIPIDIL (fenofibrate) has not been established in clinical trials of primary or secondary prevention to reduce the risk of developing coronary heart disease, LIPIDIL is not indicated for such use. (See WARNINGS and PRECAUTIONS).

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

2. Preexisting gallbladder disease.(see WARNINGS).

3. Hypersensitivity to fenofibrate.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between LIPIDIL (fenofibrate), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to LIPIDIL. In the first of these studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for 5 years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In a study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for 5 years and followed 1 year beyond. There was a statistically significant, 44% higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

   During the 5 year primary prevention component of the Helsinki Heart Study involving 4081 middle-aged males treated with either gemfibrozil or placebo, and the 3.5 year open extension, total mortality was 22% higher in the original gemfibrozil randomization group ($p=0.19$, 95% confidence interval for relative risk G:P=0.91-1.64). Cancer deaths trended higher in the gemfibrozil group ($p=0.11$), while cancers (excluding basal cell carcinoma) were diagnosed in 2.5% of patients in both treatment groups. Because of the more limited size of the Helsinki

Heart Study, the relative risk of death from any cause did not differ statistically from the relative risk of 1.29 clofibrate/placebo observed at the 9 year follow-up of the WHO study. Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group (0.9% vs. 0.5% with placebo) did not differ statistically from the excess observed in the clofibrate group compared to placebo in the WHO study.

The secondary prevention component of the Helsinki Heart Study involved 628 middle-aged males excluded from the primary prevention study because of known or suspected coronary heart disease and treated with either gemfibrozil or placebo for 5 years. Cardiac deaths trended higher in the gemfibrozil group (17/311 vs. 8/317 placebo patients, p=0.06, hazard ratio 2.2, 95% confidence interval for hazard ratio = 0.94-5.05). Gallbladder surgery was more frequent in the gemfibrozil group (1.9% vs. 0.3%, p=0.07), as was appendectomy (6 cases on gemfibrozil vs. 0 on placebo, p=0.029).

2. Liver Function: Fenofibrate use at doses of 200 to 300 mg/day is associated with significant increases in serum transaminases [AST (SGOT) or ALT (SPGT)]. Increases to > 3 times the upper limit of normal occurred in 6.3% of LIPIDIL-treated patients taking 200 to 300 mg/day in controlled multiple-dose trials lasting 8-24 weeks.

Patients with AST or ALT > 3x the Upper Normal Limits in
Controlled Clinical Trials vs Fenofibrate (200 to 300 mg/day)

	N	# Events	Events Rate
Control	336	4	1.2%
Fenofibrate	442	28	6.3%

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. However, the transaminase determinations remained above normal limits in 2 of the 28 patients (7.1%) at the end of follow-up off treatment. Fenofibrate hepatotoxicity appears to be dose-related. In an 8-week dose-ranging study the incidence of ALT or AST elevations at least three times the upper limit of normal was 13% in patients receiving 200 or 300 mg/day and was 0% in those receiving 100 or 50 mg/day, or placebo. Both hepatocellular and cholestatic hepatitis have been reported. In literature reports, hepatitis associated with fenofibrate has occurred after exposures of weeks to several years.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with LIPIDIL, and therapy discontinued if enzyme levels persist above three times the normal limit.

3. Cholelithiasis. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the gemfibrozil treatment group. Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. LIPIDIL therapy should be discontinued if gallstones are found.

4. Concomitant Oral Anticoagulants. Caution should be exercised when anticoagulants are given in conjunction with LIPIDIL because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with LIPIDIL and HMG-CoA reductase inhibitors (such as lovastatin, pravastatin, and simvastatin). No data exists on this combined therapy. The association of the chemically and pharmacologically related similar compound gemfibrozil and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

   In virtually all patients who have had an unsatisfactory lipid response to either drug alone, any potential lipid benefit of combined therapy with HMG CoA reductase inhibitors and LIPIDIL does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. The use of fibrates alone, including LIPIDIL, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving LIPIDIL and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, LIPIDIL therapy should be stopped.

6. The effect of LIPIDIL on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. LIPIDIL should be administered only to those patients described under INDICATIONS AND USAGE. If a significant reduction in fasting chylomicronemia does not occur, LIPIDIL should be discontinued.

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PRECAUTIONS

1. Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting LIPIDIL therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

2. Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of LIPIDIL. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 300 mg/day.

3. Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy or a secondary phenomenon through biliary tract stone or sludge formation and obstruction of the common bile duct.

4. Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with LIPIDIL. Urticaria was seen in 1.25 vs 0%, and rash in 2.82 vs 1.23% of fenofibrate and placebo patients respectively in controlled trials.

5. Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of LIPIDIL therapy. However, these levels stabilise during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of LIPIDIL administration.

6. Skeletal muscle: The use of fibrates alone, including LIPIDIL may occasionally be associated with myositis. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatinine phosphokinase levels.

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Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

7. Drug interactions:

(A) Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LIPIDIL. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

(B) HMG-CoA reductase inhibitors: Rhabdomyolysis has occurred when lovastatin was administered in combined therapy with gemfibrozil, a compound of the fibrate class related to fenofibrate. In most patients who have had an unsatisfactory lipid response to either drug alone, any possible benefit of combined therapy with an HMG-CoA reductase inhibitor and LIPIDIL is not outweighed by the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(C) Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take LIPIDIL at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

(D) Cyclosporin: Because cyclosporin can produce nephrotoxicity with decrease in creatine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including LIPIDIL, there is a risk that an interaction will lead to deterioration. The benefits and risks of using LIPIDIL with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

8. Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum

recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

9. **Pregnancy Category C:** Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

10. Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

11. Use in Children: Safety and efficacy in children have not been established.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 1% or more of patients treated with LIPIDIL during the six month and the eight week double-blind, placebo-controlled trials in the U.S.[1,3] are listed in the table below. Adverse events led to discontinuation of treatment in 6% of patients treated with LIPIDIL and in 2% treated with placebo. Skin rashes were the most frequent events, causing discontinuation of LIPIDIL treatment in 2% of patients in double-blind trials.

BODY SYSTEM Adverse Event	LIPIDIL (N = 191)	PLACEBO (N = 183)
BODY AS A WHOLE		
Asthenia/Fatigue	5%	3%
Infections	18%	15%
Flu Syndrome	5%	2%
Localized/Misc. Pain	8%	7%
Headache	5%	4%
CARDIOVASCULAR		
Arrhythmia	1%	1%
DIGESTIVE		
Dyspepsia	5%	7%
Eructation	1%	0%
Flatulence	3%	2%
Nausea/Vomiting	4%	3%
Abdominal Pain	3%	3%
Constipation	3%	2%
Diarrhea	3%	7%
MUSCULOSKELETAL		
Arthralgia	3%	4%
NERVOUS		
Decreased Libido	2%	1%
Paresthesia	1%	2%
Increased Appetite	1%	1%
Dizziness	2%	1%
Insomnia	1%	1%
RESPIRATORY		
Cough	1%	1%
Rhinitis	4%	3%
Sinusitis	1%	1%
SKIN & APPENDAGES		
Pruritus	3%	1%
Rash	6%	2%
SPECIAL SENSES		
Earache	1%	1%
Eye Floaters	1%	0%
Blurred Vision	1%	1%
Conjunctivitis	1%	2%
Eye Irritation	2%	1%
UROGENITAL		
Polyuria	1%	1%
Vaginitis	1%	1%

Additional clinical adverse events reported by fewer than 1% of patients in the U.S. double-blind studies, those reported in other clinical trials, and spontaneously reported in post-marketing surveillance outside the U.S. are listed below, categorized by causality:

PROBABLY CAUSALLY RELATED: Digestive: hepatitis, cholelithiasis, cholecystitis, hepatomegaly; Musculoskeletal: myalgia, myasthenia, rhabdomyolysis; Skin and appendages: photosensitivity, eczema; Respiratory: allergic pulmonary alveolitis.

CAUSAL RELATIONSHIP NOT ESTABLISHED: Body as a whole: facial edema, weight decrease, fever, epistaxis; Cardiovascular: peripheral edema, angina, palpitations, tachycardia, migraine; Digestive: hematemesis, pancreatitis; Respiratory: congestion; Nervous: dry mouth, vertigo, anxiety, sleep disorders, confusion; Skin and appendages: lupus-like syndrome, ichthyosis, telangiectasis, alopecia; Special senses: amblyopia, tinnitus; Urogenital: decreased male fertility, renal lithiasis.

LABORATORY: In the two U.S. placebo controlled studies, serum transaminase determinations (SGPT and/or SGOT) were increased to over three times the upper normal limit in 5 to 10% of patients taking Lipidil at doses of 300 mg/day (See WARNINGS). Other changes that occurred more frequently during Lipidil treatment compared to placebo included increases in creatinine and blood urea, and decreases in hemoglobin and uric acid.

Additional laboratory findings that have been reported during fenofibrate treatment that are probably causally related include: anemia, leucopenia, eosinophilia, thrombocytopenia, and increased creatinine phosphokinase.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate triglyceride-lowering diet before receiving LIPIDIL, and should continue this diet during treatment with LIPIDIL.

LIPIDIL should be given with meals. The initial dose is usually 100 mg per day, depending on the physician's assessment of the patient's risk for pancreatitis (see INDICATIONS AND USAGE). Dosage should be individualized according to patient response, and should be increased sequentially if necessary following repeat serum triglyceride estimations at 4-to-8 week intervals. The maximum dose is 300 mg/day.

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Treatment with LIPIDIL should be initiated at a dose of 100 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and triglyceride levels at this dose. In the elderly, the initial dose should likewise be limited to 100 mg/day.

OVERDOSAGE

Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

LIPIDIL (fenofibrate) is available as opaque white hard gelatin capsules. Each capsule contains 100 mg fenofibrate. Each capsule is printed with "LIPIDIL". LIPIDIL is available in bottles of 90 and bottles of 1000.

NDC 0087-0709-41	Bottles of 90
NDC 0087-0709-03	Bottles of 1000

STORAGE

Store in a cool dry place. Protect from temperatures above 30°C (86°F). Avoid excessive light and humidity.

Distributed by

FOURNIER RESEARCH INC.
609 Mamaroneck Avenue
P.O.Box 340
MAMARONECK
N.Y. 10543

CAUTION—Federal law prohibits dispensing without prescription.

Revised: November 12, 1993

REFERENCES

1. Goldberg AC, et al: Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. Clinical Therapeutics 11: 69-83, 1989.

2. Nikkila EA: Familial Lipoprotein Lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J.B. et al. (eds.): The Metabolic Basis of Inherited Disease, 5th edition, Mc Graw - Hill, 1983, Chap. 30, pp. 622-642

3. Brown WV, et al: Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study in Patients with Type IIA or IIB Hyperlipidemia. Arteriosclerosis 6: 670-678, 1986.

B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-304/S005

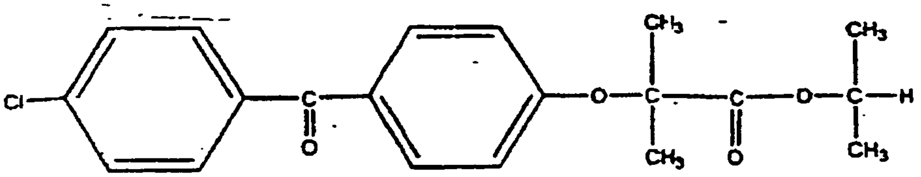
FINAL PRINTED LABELING

(Nos. 4342,6415, 6447)
NEW

TRICOR®
(fenofibrate capsules), micronized

R_x Only

DESCRIPTION
TRICOR (fenofibrate capsules), micronized, is a lipid regulating agent available as capsules for oral administration. Each capsule contains 67 mg, 134 mg or 200 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83: fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.
Inactive Ingredients: Each capsule also contains crospovidone, iron oxide, lactose, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide.

CLINICAL PHARMACOLOGY
A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Clinical experience has been obtained with two different formulations of fenofibrate: a "micronized" and "non-micronized" formulation, which have been demonstrated to be bioequivalent. Comparisons of blood levels following oral administration of both formulations in healthy volunteers demonstrate that a single capsule containing 67 mg of the "micronized" formulation is bioequivalent to 100 mg of the "non-micronized" formulation. Three capsules containing 67 mg TRICOR are bioequivalent to a single 200 mg TRICOR capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With micronized fenofibrate, the absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with single oral doses equivalent to 67 mg TRICOR and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 200 mg TRICOR per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1
Mean Percent Change in Lipid Parameters at End of Treatment[*]

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%•	-20.6%•	+11.0%•	-28.9%•
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%•	-31.4%•	+9.8%•	-23.5%•
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%•	-20.1%•	+14.6%•	-35.9%•
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

[*] Duration of study treatment was 3 to 6 months.
• p = <0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)
The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials[1] of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 200 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2
Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	Placebo				TRICOR			
Baseline TG levels 350 to 499 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*
Study 2	**Placebo**				**TRICOR**			
Baseline TG levels 500 to 1500 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

* = $p<0.05$ vs Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet for the reduction of LDL-C, Total-C, Triglycerides and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

Type	Lipoprotein Elevated	Lipid Elevation	
		Major	Minor
I (rare)	chylomicrons	TG	1-C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	---
IV	VLDL	TG	1-C
V (rare)	chylomicrons, VLDL	TG	↑–

C =cholesterol.
TG=triglycerides
LDL=low density lipoprotein
VLDL=very low density lipoprotein
IDL=intermediate density lipoprotein

The NCEP Treatment Guidelines

Definite Athlerosclerotic Disease[a]	Two or More Other Risk Factors[b]	LDL-Cholesterol mg/dL (mmol/L)	
		Initiation Level	Goal
No	No	≥ 190 (≥ 4.9)	< 160 (< 4.1)
No	Yes	≥ 160 (≥ 4.1)	< 130 (< 3.4)
Yes	Yes or No	≥ 130[c] (≥ 3.4)	< 100 (< 2.6)

(a) Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).
(b) Other risk factors for coronary heart disease (CHD) include age (males, ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD, current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L), and diabetes mellitus. Subtract 1 risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L)
(c) In CHD patients with LDL-C levels 100 to 129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 134 mg to 200 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose-related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 134 mg to 200 mg TRICOR per day and was 0% in those receiving dosages equivalent to 34 mg or 67 mg TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of TRICOR and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate capsules), micronized, Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 200 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson Syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: **CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.**

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg: 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg: 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg: 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate: hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 200 mg TRICOR
** Significantly different from Placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.
CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.
DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, nausea, vomiting, and diarrhea.
ENDOCRINE SYSTEM: Diabetes mellitus
HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.
METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.
MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, parasthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.
RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.
SKIN AND APPENDAGES: Rash, pruritis, eczema, herpes zoster, urticaria, acne. sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.
SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.
UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal. urolithiasis, gynocomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR should be given with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 200 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 67 to 200 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 200 mg per day.

Treatment with TRICOR should be initiated at a dose of 67 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 67 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR® (fenofibrate capsules), micronized, is available as hard gelatin capsules in three strengths:

67 mg yellow capsules, imprinted with on cap and Abbo-Code identification letters FR on body, available in bottles of 90 (NDC 0074-4342-90) and Abbo-Pac packages of 100 (NDC 0074-4342-11).

134 mg white capsules, imprinted with on cap and Abbo-Code identification letters AR on body, available in bottles of 90 (NDC 0074-6447-90) and Abbo-Pac packages of 100 (NDC 0074-6447-11).

200 mg orange capsules, imprinted with on cap and Abbo-Code identification letters SR on body, available in bottles of 90 (NDC 0074-6415-90) and Abbo-Pac packages of 100

(NDC 0074-6415-11).

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Laboratoires Fournier, S.A., 21300 Chenôve, France

Made in France

REFERENCES

1. GOLDBERG AC, *et al*. Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics*, 11, pp. 69-83, 1989.
2. NIKKILA ~~EA.~~ Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., *et al*. (eds.): *The Metabolic Basis of Inherited Disease*, 5th edition. McGraw-Hill, 1983, Chap. 30, pp. 622-642.
3. BROWN WV. *et al*. Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis*. 6, pp. 670-678, 1986.

Revised: March, 2000

ABBOTT
LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

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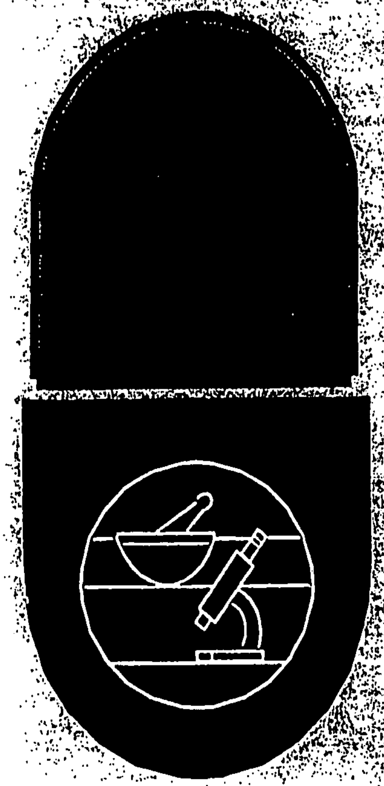

APPROVED DRUG PRODUCTS

WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

22nd EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER
SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT AND SERVICES

2002

FELBAMATE

SUSPENSION; ORAL
FELBATOL

	+ WALLACE LABS	600MG/5ML	N20189 003	JUL 29, 1993

TABLET; ORAL
FELBATOL

	WALLACE LABS	400MG	N20189 001	JUL 29, 1993
	+	600MG	N20189 002	JUL 29, 1993

FELODIPINE

TABLET, EXTENDED RELEASE; ORAL
PLENDIL

	ASTRAZENECA	2.5MG	N19834 004	SEP 22, 1994
		5MG	N19834 001	JUL 25, 1991
	+	10MG	N19834 002	JUL 25, 1991

FELODIPINE; *MULTIPLE*

SEE ENALAPRIL MALEATE; FELODIPINE

FENOFIBRATE

CAPSULE; ORAL
TRICOR (MICRONIZED)

	ABBOTT	67MG	N19304 002	FEB 09, 1998
		134MG	N19304 003	JUN 30, 1999
	+	200MG	N19304 004	JUN 30, 1999

TABLET; ORAL
TRICOR

	ABBOTT	54MG	N21203 001	SEP 04, 2001
	+	160MG	N21203 003	SEP 04, 2001

FENOLDOPAM MESYLATE

INJECTABLE; INJECTION
CORLOPAM

	+ ABBOTT	EQ 10MG BASE/ML	N19922 001	SEP 23, 1997

FENOPROFEN CALCIUM

CAPSULE; ORAL
FENOPROFEN CALCIUM

AB	GENEVA PHARMS	EQ 200MG BASE	N72394 001	OCT 17, 1988
AB		EQ 300MG BASE	N72395 001	OCT 17, 1988
AB	PAR PHARM	EQ 200MG BASE	N72437 001	AUG 22, 1988
AB		EQ 300MG BASE	N72438 001	AUG 22, 1988
	NALFON			
AB	+ DISTA	EQ 300MG BASE	N17604 002	
	NALFON 200			
AB	DISTA	EQ 200MG BASE	N17604 003	

TABLET; ORAL
FENOPROFEN CALCIUM

AB	DANBURY PHARMA	EQ 600MG BASE	N72602 001	OCT 11, 1988
AB	GENEVA PHARMS	EQ 600MG BASE	N72396 001	OCT 17, 1988
AB	IVAX PHARMS	EQ 600MG BASE	N72557 001	AUG 29, 1988
AB	LEDERLE	EQ 600MG BASE	N72326 001	AUG 17, 1988
AB	MUTUAL PHARM	EQ 600MG BASE	N72902 001	DEC 21, 1990
AB	MYLAN	EQ 600MG BASE	N72267 001	AUG 17, 1988
AB	PAR PHARM	EQ 600MG BASE	N72429 001	AUG 17, 1988
AB	PUREPAC PHARM	EQ 600MG BASE	N72274 001	MAY 02, 1988
AB	WATSON LABS	EQ 600MG BASE	N72407 001	AUG 17, 1988
	NALFON			
AB	+ DISTA	EQ 600MG BASE	N17710 001	

PRESCRIPTION AND OTC DRUG PRODUCT
PATENT AND EXCLUSIVITY DATA

APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT EXPIRES	USE CODE	EXCLUS CODE	EXCLUS EXPIRES
020801 001	FAMOTIDINE;PEPCID AC	5667794	MAY 02, 2015			
		5854267	DEC 29, 2015	U-267		
		5075114	DEC 24, 2008			
		5075114*PED	JUN 24, 2009			
		5667794*PED	NOV 02, 2015			
		5854267*PED	JUN 29, 2016			
020902 001	FAMOTIDINE;PEPCID AC	5854267	DEC 29, 2015	U-368	PED	MAY 09, 2002
		5854267*PED	JUN 29, 2016	U-368		
		5667794	MAY 02, 2015	U-368		
		5667794*PED	NOV 02, 2015	U-368		
		4820524	FEB 20, 2007			
		4820524*PED	AUG 20, 2007			
020189 001	FELBAMATE;FELBATOL	4978680	SEP 26, 2009	U-83		
		5082861	SEP 26, 2009	U-83		
020189 002	FELBAMATE;FELBATOL	4978680	SEP 26, 2009	U-83		
		5082861	SEP 26, 2009	U-83		
020189 003	FELBAMATE;FELBATOL	4978680	SEP 26, 2009	U-83		
		5082861	SEP 26, 2009	U-83		
019834 001	FELODIPINE;PLENDIL	4803081	APR 03, 2007			
		4803081*PED	OCT 03, 2007			
019834 002	FELODIPINE;PLENDIL	4803081	APR 03, 2007			
		4803081*PED	OCT 03, 2007			
019834 004	FELODIPINE;PLENDIL	4803081	APR 03, 2007			
		4803081*PED	OCT 03, 2007			
021203 001	FENOFIBRATE;TRICOR	4895726	JAN 19, 2009		I-298	APR 24, 2003
		6277405	JAN 09, 2018			
		6074670	JAN 09, 2018			
021203 003	FENOFIBRATE;TRICOR	4895726	JAN 19, 2009		I-298	APR 24, 2003
		6277405	JAN 09, 2018			
		6074670	JAN 09, 2018			
019304 002	FENOFIBRATE;TRICOR (MICRONIZED)	4895726	JAN 19, 2009		I-298	APR 24, 2003
019304 003	FENOFIBRATE;TRICOR (MICRONIZED)	4895726	JAN 19, 2009		I-298	APR 24, 2003
019304 004	FENOFIBRATE;TRICOR (MICRONIZED)	4895726	JAN 19, 2009		I-298	APR 24, 2003
019922 001	FENOLDOPAM MESYLATE;CORLOPAM				NCE	SEP 23, 2002
020747 001	FENTANYL CITRATE;ACTIQ	4671953	MAY 01, 2005	U-253		
020747 002	FENTANYL CITRATE;ACTIQ	4671953	MAY 01, 2005	U-253		
020747 003	FENTANYL CITRATE;ACTIQ	4671953	MAY 01, 2005	U-253		
020747 004	FENTANYL CITRATE;ACTIQ	4671953	MAY 01, 2005	U-253		
020747 005	FENTANYL CITRATE;ACTIQ	4671953	MAY 01, 2005	U-253		
020747 006	FENTANYL CITRATE;ACTIQ	4671953	MAY 01, 2005	U-253		
020195 001	FENTANYL CITRATE;FENTANYL	4671953	MAY 01, 2005	U-87		
020195 002	FENTANYL CITRATE;FENTANYL	4671953	MAY 01, 2005	U-87		
020195 003	FENTANYL CITRATE;FENTANYL	4671953	MAY 01, 2005	U-87		
020195 007	FENTANYL CITRATE;FENTANYL	4671953	MAY 01, 2005	U-87		
019813 001	FENTANYL;DURAGESIC	4588580	JUL 23, 2004	U-43		
019813 002	FENTANYL;DURAGESIC	4588580	JUL 23, 2004	U-43		
019813 003	FENTANYL;DURAGESIC	4588580	JUL 23, 2004	U-43		

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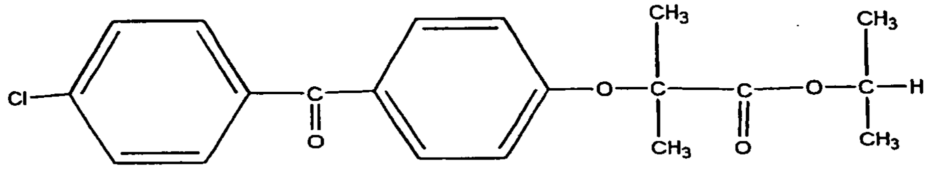
TRICOR®
(fenofibrate tablets)

R_x Only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 54 mg or 160 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, and xanthan gum.

In addition, individual tablets contain:

54 mg tablets: D&C Yellow No. 10, FD&C Yellow No. 6, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of 54 mg and 160 mg tablets are equivalent under fed conditions to 67 and 200 mg capsules, respectively.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With fenofibrate tablets, the extent of absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 160 mg TRICOR per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1
Mean Percent Change in Lipid Parameters at End of Treatment[†]

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

[†] Duration of study treatment was 3 to 6 months.
* p = <0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)
The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials[1] of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 160 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2
Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	**Placebo**				**TRICOR**			
Baseline TG levels 350 to 499 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*
Study 2	**Placebo**				**TRICOR**			
Baseline TG levels 500 to 1500 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

* = $p<0.05$ vs. Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

		Lipid Elevation	
Type	**Lipoprotein Elevated**	**Major**	**Minor**
I (rare)	chylomicrons	TG	↑↔C
IIa	LDL	C	-
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	-
IV	VLDL	TG	↑↔C
V (rare)	chylomicrons, VLDL	TG	↑↔

C=cholesterol
TG=triglycerides
LDL=low density lipoprotein
VLDL=very low density lipoprotein
IDL=intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	**LDL Goal (mg/dL)**	**LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)**	**LDL Level at Which to Consider Drug Therapy (mg/dL)**
CHD† or CHD risk equivalents (10-years risk >20%)	<100	≥100	≥130 (100-129:drug optional)††
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk Factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD = coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 107 mg to 160 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.-

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 107 mg to 160 mg TRICOR per day and was 0% in those receiving dosages equivalent to 54 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of TRICOR and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.
Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 160 mg per day.
Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.
Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.
Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.
Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.
HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).
Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take

TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60%

increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo.. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%

SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 200 mg TRICOR

**. Significantly different from Placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.
CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.
DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.
ENDOCRINE SYSTEM: Diabetes mellitus
HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.
METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.
MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.
NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.
RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.
SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.
SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.
UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR tablets should be given with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 160 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 54 to 160 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 160 mg per day.

Treatment with TRICOR should be initiated at a dose of 54 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 54 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR™ (fenofibrate tablets) is available in two strengths:

54 mg yellow tablets, imprinted with a and Abbo-Code identification letters "TA", available in bottles of 90 (**NDC** 0074-4009-90).

160 mg white tablets, imprinted with a and Abbo-Code identification letters "TC", available in bottles of 90 (**NDC** 0074-4013-90).

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Laboratoires Fournier, S.A., 21300 Chenôve, France

Made in France

REFERENCES

1. GOLDBERG AC, *et al.* Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics*, 11, pp. 69-83, 1989.
2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., *et al.* (eds.): *The Metabolic Basis of Inherited Disease*, 5th edition, McGraw-Hill, 1983, Chap. 30, pp. 622-642.
3. BROWN WV, *et al.* Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis*. 6, pp. 670-678, 1986.

Revised: NEW

ABBOTT
LABORATORIES
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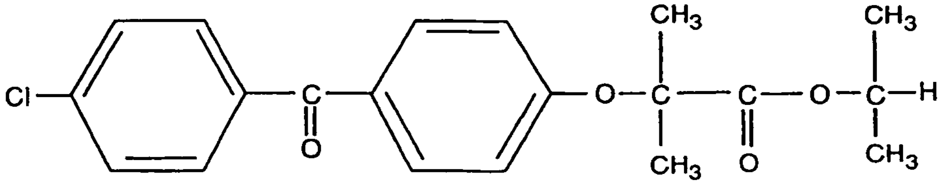
TRICOR® 48 mg and 145 mg

(fenofibrate tablets)

℞ only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 48 mg or 145 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains hypromellose 2910 (3cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate.

In addition, individual tablets contain:

48 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D&C Yellow #10 aluminum lake, FD&C Yellow #6 /sunset yellow FCF aluminum lake, FD&C Blue #2 /indigo carmine aluminum lake.

145 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

Exposure to fenofibric acid in plasma, [illegible] measured by C_{max} and AUC, is not significantly different when a single 145 mg dose of fenofibrate is administered under fasting or nonfasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) with pravastatin (40 mg) once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively in 23 healthy adults.

A single dose of pravastatin had no clinically important effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) with atorvastatin (20 mg) once daily for 10 days resulted in approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 145 mg TRICOR (fenofibrate tablets) per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1
Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

† Duration of study treatment was 3 to 6 months.
* p = < 0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)
The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials[1] of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 145 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2
Effects of TRICOR in Patients With Fredrickson
Type IV/V Hyperlipidemia

Study 1	Placebo				TRICOR			
Baseline TG levels 350 to 499 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*
Study 2	**Placebo**				**TRICOR**			
Baseline TG levels 500 to 1500 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

*= p < 0.05 vs. Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

Type	Lipoprotein Elevated	Lipid Elevation	
		Major	Minor
I (rare)	chylomicrons	TG	↑↔C
IIa	LDL	C	-
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	-
IV	VLDL	TG	↑↔C
V (rare)	chylomicrons, VLDL	TG	↑↔C

C = cholesterol
TG = triglycerides
LDL = low density lipoprotein
VLDL = very low density lipoprotein
IDL = intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[†] or CHD risk equivalents (10-years risk > 20%)	< 100	≥ 100	≥ 130 (100-129:drug optional)[††]
2+ Risk Factors (10-year risk ≤ 20%)	< 130	≥ 130	10-year risk 10%-20%: ≥ 130 10-year risk < 10%: ≥ 160
0-1 Risk Factor[†††]	< 160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)

[†] CHD = coronary heart disease

[††] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

[†††] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieve[illegible] the TG is still >200 mg/dL, non HDL-C (t[illegible] minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are 30 mg/dL higher than LDL-C goals for each [illegible] category.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 96 mg to 145 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 96 mg to 145 mg TRICOR per day and was 0% in those receiving dosages equivalent to 48 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also **CLINICAL PHARMACOLOGY**, Drug-drug interactions).

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically signi [illegible] etween study groups, but did trend higher in [illegible] nfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfi[illegible] group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 145 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR (fenofibrate tablets) with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD) of 145 mg/day, based on mg/meter^2 of surface area). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/meter^2 surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and Gemfibrozil (250 mg/kg/day; 2 times the human dose) (multiples based on mg/meter^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the MRHD on the basis of mg/meter^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at the same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to [illegible]oid of mutagenic potential in the followin[illegible]: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of approximately 9 times the MRHD of 145mg/day of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 10 times the MRHD to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of approximately 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of fenofibrate at 9 to 18 times the MRHD to female rabbits caused abortions in 10% to 25% of dams and death in 7% of fetuses at 18 times the MRHD.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 145 mg TRICOR

** Significantly different from Placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.

CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

DIGESTIVE SYSTEM: Dyspepsia, flat nausea, increased appetite, gastroenteritis elithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodena er, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.
ENDOCRINE SYSTEM: Diabetes mellitus.
HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.
METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.
MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.
NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.
RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, allergic pulmonary alveolitis, pneumonia, laryngitis, and sinusitis.
SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.
SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.
UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, abnormal kidney function, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR tablets can be given without regard to meals.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 145 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 48 to 145 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 145 mg per day.

Treatment with TRICOR should be initiated at a dose of 48 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 48 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR® (fenofibrate tablets) is available in two strengths:

48 mg yellow tablets, imprinted with a and Abbo-Code identification letters "FI", available in bottles of 90 (NDC 0074-6122-90).

145 mg white tablets, imprinted with a and Abbo-Code identification letters "FO", available in bottles of 90 (NDC 0074-6123-90).

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Fournier Laboratories Ireland Limited, Anngrove, Carrigtwohill Co. Cork, Ireland

REFERENCES

1. GOLDBERG AC, *et al.* Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics,* 11, pp. 69-83, 1989.
2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., *et al.* (eds.): *The Metabolic Basis of Inherited Disease,* 5th edition, McGraw-Hill, 1983, Chap. 30, pp. 622-642.
3. BROWN WV, *et al.* Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis.* 6, pp. 670-678, 1986.

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04K-030-F542-1 MASTER

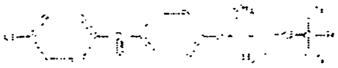
ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.

F

Antara™
(fenofibrate) Capsules

DESCRIPTION

Antara (fenofibrate) Capsules, is a lipid regulating agent available as capsules for oral administration. Each capsule contains 43 mg, 87 mg, or 130 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79°-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each gelatin capsule contains sugar spheres, hypromellose, sodium lauryl sulfate, dimethicone, simethicone, and talc. The gelatin capsules also contain sulfur dioxide, titanium dioxide, yellow iron oxide, Indigo carmine FD&C Blue #2, D&C Yellow #10 and black ink.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides, and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apo AI and apo AII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α ($PPAR_\alpha$).

Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of $PPAR_\alpha$ also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after multiple dose administration of Antara 130 mg capsules are equivalent, under low-fat fed conditions, to 200 mg fenofibrate capsules.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid from Antara occur within 4 to 8 hours after administration.

There was less than dose-proportional increase in the systemic exposure of fenofibric acid from three strengths (43 mg, 87 mg, and 130 mg) of Antara under fasting conditions.

Doses of two- or three-capsules of 43 mg Antara given concurrently were dose-equivalent to single-capsule doses of 87 mg and 130 mg, respectively.

The extent of absorption of acid was unaffected when Antara was taken either in fasted state or with a low-fat meal. However, the C_{max} of Antara increased in the presence of a low-fat meal. T_{max} was unaffected in the presence of a low-fat meal. In the presence of a high-fat meal, there was a 26% increase in AUC and 108% increase in C_{max} of fenofibric acid from Antara relative to fasting state.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within a week of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibrate acid from Antara is eliminated with a half-life of 23 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77–87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

Antara has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied; however, fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance <50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of Antara should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption (see WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 130 mg Antara per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1.
Mean Percent Change in Lipid Parameters at End of Treatment[†]

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C >160 mg/dL and TG <150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C >160 mg/dL and TG≥150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.5%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

[†] Duration of study treatment was 3 to 6 months.

* p=<0.05 vs. placebo

In a subset of the subjects, measurements of apo B were conducted. Fenofibrate treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 130 mg Antara per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2.
Effects of Fenofibrate in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	Placebo				Fenofibrate			
Baseline TG levels 350 to 499 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*

Study 2	Placebo				Fenofibrate			
Baseline TG levels 500 to 1500 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	14	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	13.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

*=p<0.05 vs. placebo

The effect of fenofibrate on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

Antara is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides, and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

Antara is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. >2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of Antara therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet (see WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

Type	Lipoprotein Elevated	Lipid Elevation Major	Minor
I (rare)	Chylomicrons	TG	↑↔C
IIa	LDL	C	–
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	–
IV	VLDL	TG	↑↔C
V (rare)	Chylomicrons, VLDL	TG	↑↔

C=cholesterol
TG=triglycerides
LDL=low density lipoprotein
VLDL=very low density lipoprotein
IDL=intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[†] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)[††]
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk Factor[†††]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[†] CHD=coronary heart disease.

[††] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

[†††] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

Antara is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

Fenofibrate is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 87 mg to 130 mg Antara per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 87 mg to 130 mg Antara per day and was 0% in those receiving dosages equivalent to 43 mg or less Antara per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with Antara, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Antara therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with Antara because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.
Concomitant HMG-CoA Reductase Inhibitors: The combined use of Antara and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of fenofibrate and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin, or its active metabolite 3α-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including Antara may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving Antara and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, Antara therapy should be stopped.
Mortality: The effect of Antara on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.
Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to Antara.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial Therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting Antara therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.
Continued Therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of Antara. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 130 mg per day.
Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.
Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients, respectively, in controlled trials.
Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of Antara administration.
Skeletal Muscle: The use of fibrates alone, including Antara, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase (CPK) levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions:
Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ANTARA. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.
HMG-CoA Reductase Inhibitors: The combined use of Antara and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).
Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take Antara at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.
Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including Antara, there is a risk that an interaction will lead to deterioration. The benefits and risks of using Antara with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.
Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter² of surface area) the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter² surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter² surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter² surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration, and unscheduled DNA synthesis.
Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter² surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.
Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.
Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM Adverse Event	Fenofibrate* (N=439)	Placebo (N=365)
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4%**	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 130 mg Antara
** Significantly different from placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.
BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.
CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.
DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.
ENDOCRINE SYSTEM: Diabetes mellitus.
HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.
METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.
MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.
NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.
RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis
SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.
SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.
UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with Antara. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Antara, and should continue this diet during treatment with Antara. Antara capsules should be taken with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of Antara is 130 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 43 to 130 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 130 mg per day.

Treatment with Antara should be initiated at a dose of 43 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 43 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of Antara if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

Antara (fenofibrate) Capsules, is available in three strengths:

43 mg capsules, imprinted with "43" and a segmented band, on the light green cap and "ANTARA" with the Reliant logo on the white to off-white body, available in bottles of 30 (NDC # 65726-401-10) and 100 (NDC # 65726-401-25).

87 mg capsules, imprinted with "87" and a segmented band, on the dark green cap and "ANTARA" with the Reliant logo on the light green body, available in bottles of 30 (NDC # 65726-402-10) and 100 (NDC # 65726-402-25).

130 mg capsules, imprinted with "130" and a segmented band, on the dark green cap and "ANTARA" with the Reliant logo on the white body, available in bottles of 30 (NDC # 65726-403-10) and 100 (NDC # 65726-403-25).

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature] in a tightly closed container.

REFERENCES:
1. GOLDBERG AC, *et al.* Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics.* 11 pp 69-83, 1989.

2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., *et al.* (eds.): *The Metabolic Basis of Inherited Disease.* 5th edition, McGraw-Hill, 1983, Chap. 30, pp. 622-642.

3. BROWN WV, *et al.* Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis.* 6. pp 670-678, 1986

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